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Therapeutic Class Review
Miscellaneous Cardiac Drugs

I. Overview

Ranolazine is currently the only agent classified as a miscellaneous cardiac drug via the American Hospital Formulary Service (AHFS).[1] It is Food and Drug Administration (FDA) approved for the treatment of chronic angina. It may be used alone or in combination with calcium channel blockers, β-blockers, nitrates, anti-platelet therapy, lipid-lowering therapy, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs).[2] It does not abate an acute angina episode, but rather is designed to minimize or prevent recurrent episodes from occurring. The mechanism of action of ranolazine is unknown. It is suggested that ranolazine inhibits the slow sodium channel in the cardiac muscle, thereby reducing sodium/calcium exchange and preventing the accumulation of calcium and diastolic stiffness.[3] This in turn improves myocardial perfusion. Unlike other antianginal agents, ranolazine does not reduce heart rate or blood pressure. At maximal exercise, it does not increase the rate-pressure product, which is a measure of myocardial work.[4] However, ranolazine exhibits a dose-related QT interval prolongation and therefore can increase the risk of arrhythmias. While an increased risk of arrhythmias or sudden death has not been demonstrated in patients with an acute coronary syndrome, there is limited experience with doses exceeding the maximum recommended dose (>1000 mg twice daily), coadministration with other QT-prolonging drugs, or potassium channel supplements.

Angina occurs when the myocardial oxygen demand exceeds the oxygen supply, resulting in chest discomfort or pain. The currently available treatment options for chronic angina include nitrates, β-blockers, and calcium-channel blocking agents (CCBs). These agents either decrease oxygen demand and/or increase oxygen supply.[5] Nitrates, such as isosorbide dinitrate, isosorbide mononitrate, and transdermal nitroglycerin, reduce cardiac oxygen demand by decreasing left ventricular pressure and systemic vascular resistance and dilating coronary arteries. However, the use of nitrates as first-line agents has been limited because of tolerance that develops with chronic use. β-Blockers, such as atenolol and metoprolol, reduce heart rate and contractility by competitively blocking the response to beta-adrenergic stimulation in the heart. β-Blockers are recommended as first-line agents in patients with stable angina since they have been shown to reduce mortality following myocardial infarction.[6] CCBs, such as amlodipine, diltiazem, and verapamil, increase oxygen supply by producing coronary and peripheral vasodilatation, decreasing atrioventricular conduction, and reducing contractility. CCBs also decrease cardiac oxygen demand by reducing systemic vascular resistance and arterial pressure.[5] CCBs are often used because they are presumed to have similar efficacy and fewer side effects when compared to β-blockers. However, short-acting CCBs have been shown to increase the risk of cardiac events in patients with hypertension and nifedipine has been shown to increase mortality following acute ischemic syndromes.[6] Differences in long-term rates of survival or myocardial infarction between classes of antianginal agents have not been studied.

Table 1 lists all the miscellaneous cardiac drugs included in this review. This review encompasses all dosage forms and strengths.

Table 1. Miscellaneous Cardiac Drugs Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)
ranolazine	sustained-release tablet	Ranexa®

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

Treatment guidelines that incorporate the miscellaneous cardiac drugs are summarized in Table 2.

Table 2. Treatment Guidelines Using the Miscellaneous Cardiac Drugs

Clinical Guideline	Recommendations
American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines: **2007 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-segment Elevation Myocardial Infarction (UA/NSTEMI) (2007)**[7]	• Sublingual nitroglycerin (NTG) 0.4 mg may be used for anginal discomfort that has not been relieved by discontinuation of activity or removal from a stressful event. Doses can be repeated every 5 minutes if needed for 3 total doses. If pain persists after 3 doses, immediate medical attention should be sought. Early Hospital Care • Oral β-adrenergic blocking agents (β-blockers) should be initiated within the first 24 hours unless contraindicated (ie, patient has 1 or more of the following: signs of heart failure, evidence of a low-output state, increased risk of cardiogenic shock, or other relative contraindications to β-blockade). • A nondihydropyridine calcium-channel blocker (CCB) (diltiazem or verapamil) should be given as first-line treatment to patients who do not have a contraindication to either of these agents and have a contraindication to a β-blocker. These agents may also be used after β-blockers and nitrates have been fully used. • Immediate-release dihydropyridine CCBs may be considered in patients with UA/NSTEMI with ongoing ischemia or hypertension in the presence of adequate β-blockade. • Angiotensin-converting enzyme inhibitors (ACEI) should be administered orally to patients who do not have a contraindication within the first 24 hours to patients with congestive heart failure, diabetes, hypertension and/or left ventricular systolic dysfunction (ejection fraction <0.40). If the patient is intolerant to an ACEI, an angiotensin receptor blocker should be administered. • At the time the patient presents with UA/NSTEMI nonsteroidal anti-inflammatory drugs, except for aspirin, should be discontinued, however β-blockers should be continued indefinitely unless contraindicated. • Ranolazine may be safely administered for symptom relief after UA/NSTEMI, but it does not appear to significantly improve underlying disease. Late Hospital Care, Hospital Discharge, and Posthospital Discharge Care • Aspirin should be used routinely in all patients, unless contraindicated. • Clopidogrel may be used when aspirin is contraindicated or not tolerated. • Combination of aspirin and clopidogrel can be used for 12 months following UA/NSTEMI. • Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are recommended. • Fibrates or niacin should be recommended if high-density lipoprotein (HDL) <40 mg/dL, or if triglycerides are elevated. • The use of ranolazine as a component of a postdischarge regimen was not addressed.
American College of Cardiology/American Heart Association (ACC/AHA): **2007 Chronic Angina Focused Update of the ACC/AHA 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[8]	• Individual recommendations in this focused update will be incorporated into future revisions and/or updates of the ACC/AHA 2002 Guideline Update for the Management of Patients with Chronic Stable Angina (2002). • It is beneficial to start and continue β-blocker therapy indefinitely in all patients who have had a myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated. • The use of ranolazine for the treatment of angina was not addressed.
American College of Cardiology/American	• Aspirin 75-325 mg should be used routinely in all patients with acute and chronic ischemic heart disease unless contraindicated. Clopidogrel may be used when aspirin is

Clinical Guideline	Recommendations
Heart Association (ACC/AHA): **2002 Guideline Update for the Management of Patients With Chronic Stable Angina (2002)**[9]	contraindicated. • β-Blockers should be considered as initial therapy for chronic stable angina. • HMG-CoA reductase inhibitors should be recommended even in mild-to-moderate elevations of low-density lipoprotein cholesterol (LDL-C). • ACEIs should be prescribed to patients with diabetes and/or left ventricular systolic dysfunction. • There is insufficient evidence for using an angiotensin receptor blocker in chronic stable angina. • Use sublingual NTG or NTG spray for immediate relief of angina. • Long-acting CCBs or long-acting nitrates may be used if β-blockers are contraindicated. • An immediate-release and short-acting dihydropyridine CCB can increase adverse cardiac events and should not be used. • A long-acting CCBs or long-acting nitrates may be used with β-blockers if initial treatment is not successful. • The use of ranolazine for the treatment of angina was not addressed. This guideline was published before ranolazine was approved for use in the United States (2006).
European Society of Cardiology: **Management of Stable Angina Pectoris (2006)**[10]	• HMG-CoA reductase inhibitor therapy should be instituted in all patients with coronary artery disease. • Fibrates or nicotinic acid may be used as adjuncts to HMG-CoA reductase inhibitor therapy. • Aspirin should be administered at a dose of 75 mg daily, unless contraindicated. • Clopidogrel may be used in patients who can not take aspirin. • ACEI therapy is indicated in patients with hypertension, heart failure, left ventricular dysfunction with or without history of prior myocardial infarction, or diabetes. • β-blockers are indicated for most patients with more than mild angina, unless contraindicated. • Short-acting nitrates may be used for prompt relief or prevention of angina, and should be offered to all patients. • Long-acting nitrates or CCBs may be considered if β-blockers are contraindicated. • If β-blocker monotherapy is insufficient, a dihydropyridine CCB may be added. • Ranolazine has not been approved for use in the European Union. It is mentioned in the guideline but no recommendations were issued concerning its use.
European Society of Cardiology: **Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-segment Elevation (2007)**[11]	• β-Blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia and are usually well tolerated. • Intravenous or oral nitrates are effective for symptom relief in the acute management of anginal episodes. • CCBs provide symptom relief in patients already receiving nitrates and β-blockers; they are useful in patients with contraindications to β-blockade and in the subgroup of patients with vasospastic angina. • Nifedipine, or other dihydropyridines, should not be used unless combined with β-blockers. • It is noted that ranolazine exerts antianginal effects by inhibiting the late sodium current and that it was not effective in reducing major cardiovascular events in Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN-TIMI) trial. • The use of ranolazine for the treatment of angina was not further addressed. Ranolazine has not been approved for use in the European Union.
American College of Physicians (ACP): **Primary Care Management of Chronic Stable Angina and Asymptomatic Suspected or Known**	• Aspirin therapy (75-325 mg daily) should be used by all patients. • Clopidogrel may be used in patients when aspirin therapy is contraindicated. • Sublingual NTG tablets or spray may be used for anginal discomfort that has not relieved by discontinuation of activity or removal from a stressful event. Doses can be repeated every 5 minutes if needed for 3 total doses. If pain persists after 3 doses, immediate medical attention should be sought. • β-blockers should be strongly considered as initial therapy, unless contraindicated.

Clinical Guideline	Recommendations
Coronary Artery Disease (2004)[12]	• HMG-CoA reductase inhibitors therapy should be recommended even in mild-to-moderate elevations of LDL-C. • ACEIs should be recommended for patients with symptomatic chronic stable angina to prevent myocardial infarction and death and to reduce symptoms of angina, and in patients with asymptomatic chronic stable angina with coronary artery disease, who also have diabetes mellitus, systolic dysfunction, or both. • Sublingual NTG or NTG spray for immediate symptomatic relief of angina. • Long-acting CCB or long-acting nitrates may be used with β-blockers if initial treatment is not successful or if β-blockers are contraindicated. • The use of ranolazine for the treatment of angina was not addressed. This guideline was published before ranolazine was approved for use in the United States (2006).

III. Indications

Food and Drug Administration (FDA)-approved indications for the miscellaneous cardiac drugs are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Miscellaneous Cardiac Drugs[3]

Drug	Indication*
Ranolazine	Ranolazine is indicated for the treatment of chronic angina.

*Ranolazine is contraindicated in patients with clinically significant hepatic impairment and in patients on potent cytochrome P450 3A (CYP3A) inhibitors and inducers.

IV. Pharmacokinetics

The pharmacokinetic parameters for the miscellaneous cardiac drugs are summarized in Table 4. Compared with normal subjects, ranolazine plasma concentrations increased about 50% in patients with renal impairment. The mean diastolic pressure was increased by 10-15 millimeters of mercury in patients with severe renal impairment.[3,13] The plasma concentration of ranolazine increased by a factor of 1.3 in patients with mild hepatic impairment and by a factor of 1.6 in patients with moderate hepatic impairment. In addition, the increases in the QT interval were larger in patients with hepatic impairment compared with normal subjects at the same plasma concentration of ranolazine.[3,14] Ranolazine is contraindicated in patients with clinically significant hepatic impairment.[3]Moreover, renal impairment may increase ranolazine plasma concentration by up to 50%.

Table 4. Pharmacokinetic Parameters of the Miscellaneous Cardiac Drugs[3,15]

Drug	Bioavailability (%)	Protein binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Ranolazine	Absorption is highly variable	62	Mainly CYP3A4 and to a lesser extent CYP2D6	Four most abundant metabolites have half-lives of 6 to 22 hours*	Fecal excretion: 25 Urinary excretion: 75	7

*Pharmacologic activity not well characterized

V. Drug Interactions

Ranolazine is primarily metabolized by the cytochrome P450 isoenzyme system and is a substrate of P-glycoprotein (P-gp). Therefore the potential for numerous drug interactions does exist. Ranolazine is contraindicated in patients concurrently taking strong inhibitors or inducers of CYP3A4. Due to the risk of QT

interval prolongation with ranolazine, caution should be used with the coadministration of other QT-prolonging drugs.[2] Significant drug interactions with the miscellaneous cardiac drugs are listed in Table 5.

Table 5. Significant Drug-Drug Interactions With the Miscellaneous Cardiac Drugs[2,3,16-17]

Drug	Significance Level	Interaction	Mechanism
Ranolazine	1	Antiarrhythmic agents (amiodarone, bretylium, disopyramide, dofetilide, ibutilide, moricizine, procainamide, quinidine, sotalol)	Concurrent administration of ranolazine and anti-arrhythmic agents can lead to additive effects of QT interval prolongation and therefore should be done with caution. The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased.
Ranolazine	1	Azole antifungals (itraconazole, ketoconazole, voriconazole)	Azole antifungals are potent inhibitors of CYP3A and therefore may increase the steady-state plasma concentration of ranolazine, increasing the risk of dose-related prolongation in the QT interval, torsades de pointes–type arrhythmias, and sudden death. Consequently, concurrent use should be avoided.
Ranolazine	1	Nefazodone	Nefazodone is a potent inhibitor of CYP3A and therefore may increase the steady-state plasma concentration of ranolazine, increasing the risk of dose-related prolongation in the QT interval, torsades de pointes–type arrhythmias, and sudden death. Consequently, concurrent use should be avoided.
Ranolazine	1	Fluconazole	Fluconazole is a moderate inhibitor of CYP3A4 and may inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation. If used concurrently, the dose of ranolazine should not exceed 500 mg twice daily.
Ranolazine	1	Diltiazem	Diltiazem is a moderate inhibitor of CYP3A4 and may inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation. If used concurrently, the dose of ranolazine should not exceed 500 mg twice daily.
Ranolazine	1	Grapefruit juice	Grapefruit juice is a moderate inhibitor of CYP3A4 and may inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation. If used concurrently, the dose of ranolazine should not exceed 500 mg twice daily.
Ranolazine	1	Macrolide and related antibiotics (azithromycin, clarithromycin, dirithromycin, erythromycin, telithromycin)	Macrolide antibiotics inhibit the metabolism of ranolazine by the CYP3A system. Concomitant use may increase the plasma levels of ranolazine and cause QT prolongation. Consequently, concurrent use should be avoided.
Ranolazine	1	Phenothiazines (thioridazine)	There is a possible additive prolongation of the QT interval when ranolazine is administered with a phenothiazine (thioridazine). Concurrent administration may lead to additive effects on QT prolongation.
Ranolazine	1	Protease inhibitors (amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir)	Protease inhibitors inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation. Consequently, concurrent use should be avoided.

Drug	Significance Level	Interaction	Mechanism
Ranolazine	1	Verapamil	Verapamil is a moderate inhibitor of CYP3A4 and may inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation. If used concurrently, the dose of ranolazine should not exceed 500 mg twice daily.
Ranolazine	1	Aprepitant	Aprepitant is a moderate inhibitor of CYP3A4 and may inhibit the metabolism of ranolazine by the CYP3A system. Concurrent administration may increase the plasma levels of ranolazine and cause QT prolongation. If used concurrently, the dose of ranolazine should not exceed 500 mg twice daily.
Ranolazine	1	Ziprasidone	There is a possible additive prolongation of the QT interval when ranolazine is administered with ziprasidone. Concurrent administration may lead to additive effects on QT prolongation.
Ranolazine	1	Potent CYP3A4 Inducers (rifampin, rifabutin, rifapentin, Phenobarbital, phenytoin, carbamazepine, St.John's wort)	Ranolazine is a substrate of P-glycoprotein and is primarily metabolized by CYP3A. The concurrent use of ranolazine and potent CYP3A and P-glycoprotein inducers may lead to significant decreases in ranolazine plasma concentrations and should therefore be avoided.

Significance Level 1=major severity

VI. Adverse Drug Events

Ranolazine has been shown to prolong the QT interval in a dose-dependent manner.[3] The relationship between ranolazine and QT interval is linear with a slope of 2.6 microseconds per 1,000 ng/mL of ranolazine. With repeated dosing of ranolazine administered at 1,000 mg twice daily, the QT interval is prolonged by 6 microseconds. In 5% of the population the prolongation of QT is 15 microseconds. In patients with hepatic dysfunction, the QT-prolonging effect is increased approximately 3-fold. The full clinical significance of this QT prolongation effect is not known. Other drugs that have the potential to prolong the QT interval have been associated with torsades de pointes-type arrhythmias and sudden death.[3]

The most common adverse drug events reported with the miscellaneous cardiac drugs are noted in Table 6. It is important to note that in placebo controlled trials approximately 6% of patients taking ranolazine discontinued the study medication compared to 3% taking placebo. Reasons for discontinuation varied but were related to the common adverse events associated with ranolazine.[3]

Table 6. Adverse Drug Events (%) Reported with the Miscellaneous Cardiac Drugs[3]

Adverse Event	Ranolazine
Cardiovascular	
Bradycardia	0.5-2
Hypotension/orthostatic hypotension	0.5-2
Palpitations	0.5-2
QT prolongation	✔
Syncope	0.7
Central Nervous System	
Confusion	≤0.5
Dizziness	1.3-6.2
Headache	3.0-5.5
Paresthesia	≤0.5
Vertigo	0.5-2
Endocrine and Metabolic	

Adverse Event	Ranolazine
Blood urea nitrogen elevations	✔
Hemoglobin A1c reduction	✔
Serum creatinine elevations	✔
Gastrointestinal	
Abdominal pain	0.5-2
Constipation	4.5-8
Dry mouth	0.5-2
Nausea	1.0-4.4
Vomiting	0.5-2
Hematologic	
Hematuria	≤0.5
Leukopenia	≤0.5
Pancytopenia	≤0.5
Thrombocytopenia	≤0.5
Respiratory	
Dyspnea	0.5-2
Pulmonary fibrosis	≤0.5
Other	
Angioedema	≤0.5
Blurred vision	≤0.5
Eosinophilia	≤0.5
Hypoesthesia	≤0.5
Peripheral edema	0.5-2
Renal failure	≤0.5
Tinnitus	0.5-2
Tremor	≤0.5

✔ Percent not specified

VII. Dosing and Administration

Ranolazine may be used alone or in combination with calcium channel blockers, β-blockers, nitrates, anti-platelet agents, lipid-lowering therapy, ACE inhibitors, and ARBs.[2] Doses of greater than 1,000 mg twice daily should not be used, as QT prolongation is dose-related.[2,3] Moreover, if taken concurrently with a moderate CYP3A inhibitor the dose of ranolazine should not exceed 500 mg twice daily.[2] While renal impairment may increase ranolazine plasma concentration by up to 50%, dosing adjustment is not necessary. Ranolazine can be taken with or without meals. It is available as a sustained-release tablet which should be swallowed whole and not crushed, broken, or chewed. Electrocardiograms should be obtained at baseline and during follow-up to monitor for effects on QT interval.[3] The usual dosing regimens for the miscellaneous cardiac drugs are summarized in Table 7.

Table 7. Usual Dosing for the Miscellaneous Cardiac Drugs[3]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Ranolazine	Initial: 500 mg twice daily Maximum: 1,000 mg twice daily	Safety and efficacy in children have not been established.	Sustained-release tablet: 500 mg 1,000 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous cardiac drugs are found in Table 8.

Table 8. Comparative Clinical Trials Using the Miscellaneous Cardiac Drugs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chaitman, Pepine, et al[18] CARISA Ranolazine 750 or 1,000 mg BID in combination with diltiazem 180 mg DAILY, atenolol 50 mg DAILY, or amlodipine 5 mg DAILY vs placebo BID in combination with diltiazem 180 mg DAILY, atenolol 50 mg DAILY, or amlodipine 5 mg DAILY	DB, MC, PC, PG, RCT Patients with symptomatic chronic angina despite treatment with diltiazem 180 mg DAILY, atenolol 50 mg DAILY, or amlodipine 5 mg DAILY	N=823 12 weeks followed by long-term open-label study of up to 39 months	Primary: Exercise duration on treadmill Secondary: Time to angina onset, time to 1 mm ST-segment depression at trough and peak, frequency of angina attacks, frequency of nitroglycerin use, survival	Primary: In the ranolazine group, exercise duration (P=0.01) was significantly increased compared to placebo. Secondary: Time to angina (no P value reported) and time to 1 mm ST-segment depression (no P value reported) were significantly increased compared with placebo. Treatment with ranolazine significantly reduced the frequency of angina attacks (3.3 vs 2.5 attacks per week for the 750 mg group; P=0.006; and 3.3 vs 2.1 attacks per week for the 1,000 mg group; P<0.001), and nitroglycerin use (no P value reported) compared with placebo. The most common adverse effects were constipation, dizziness, nausea, and asthenia (≤7.3% in the ranolazine group vs ≥0.7% in the placebo group; no P value reported). The survival rates for patients taking ranolazine were 98.4% (95% CI, 97.4% to 99.5%) at year one and 95.9% (95% CI, 94.0% to 97.7%) at year two.
Stone et al[19] ERICA Ranolazine 1,000 mg BID in combination with amlodipine 10 mg DAILY	DB, PC, PG, RCT Stable patients with coronary disease and ≥3 anginal attacks per week despite maximum recommended	N=565 6 weeks	Primary: Frequency of angina episodes per week Secondary: Average weekly nitroglycerin consumption	Primary: Angina frequency at baseline averaged 5.63 ± 0.18 episodes per week. Treatment with ranolazine significantly reduced the frequency of angina episodes per week compared with placebo (2.88 ± 0.19 vs 3.31± 0.22; P=0.028). Secondary: Nitroglycerin consumption use at baseline averaged 4.72 ± 0.21 tablets per week. Ranolazine treatment significantly reduced the use of nitroglycerin compared with placebo (2.03 ± 0.20 vs 2.68 ± 0.22; P=0.014).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo in combination with amlodipine 10 mg DAILY	dosage of amlodipine (10 mg/day)		rate, SAQ, safety as assessed by adverse events and electrocardio-gram	The SAQ scores on angina frequency were significantly improved in the ranolazine arm compared with placebo arm (*P*=0.008). There were no significant differences between treatment groups in the other SAQ measures, such as physical limitation, anginal stability, disease perception, and treatment satisfaction. Ranolazine was well tolerated.
Chaitman, Skettino, et al[20] MARISA Ranolazine 500, 1,000, or 1,500 mg BID vs placebo BID	DB, PC, RCT, XO Patients with well-documented coronary artery disease and at least 3 month history of effort angina that responded to antianginal agents	N=191 4 weeks, with long-term follow-up of up to 36 months	Primary: Exercise duration Secondary: Time to angina onset, time to 1 mm ST-segment depression at trough and peak, exercise duration at peak, long-term survival	Primary: Treatment with ranolazine at all doses resulted in significant increases in exercise duration (*P*<0.001). Secondary: Treatment with ranolazine at all doses resulted in significant increases in time to angina (*P*<0.001) and time to 1 mm ST-segment depression (*P*<0.001). No clinically significant changes in heart rate or blood pressure at rest or exercise were observed. The rates of adverse events were similar for the 500 mg and placebo group, but higher with the 1,000 and 1,500 mg groups (15.6% for placebo, 16.0% for 500 mg, 21.7% for 1,000 mg, and 34.2% for 1,500 mg; no *P* values reported). The survival rates were 96.3% (95% CI, 93.0% to 99.5%) at one year and 93.6% (95% CI, 89.3% to 98.0%) at two years.
Rousseau et al[21] Ranolazine immediate-release* 400 mg TID for 7-10 days, atenolol 100 mg DAILY for 7-10 days, and placebo DAILY for 7-10 days Trial design used all 6 possible treatment	DB, MC, PC, XO Patients with well-documented coronary artery disease and chronic angina, who were on standard doses of atenolol	N=158 21-30 days	Primary: Time to onset of angina Secondary: Time to 1 mm ST-segment depression, total exercise duration, angina frequency,	Primary: Treatment with ranolazine and atenolol both resulted in significant increases in time to angina, exercise duration, and time to 1 mm ST-segment depression when compared with placebo (*P*<0.05 for all). Secondary: There was no significant difference between ranolazine and atenolol in the time to angina (*P*=0.18), time to 1 mm ST-segment depression (*P*=0.86), angina frequency (no *P* value reported), or nitroglycerin use (no *P* value reported). However, the increase in exercise duration was significantly greater in the ranolazine group than atenolol (mean difference of 21.1 seconds, 95% CI, 6.2 to 36.0; *P*=0.006).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sequences and each treatment period lasted 7-10 days.			nitroglycerin use	
Timmis et al[22] Ranolazine 750 or 1,000 mg BID plus atenolol 50 mg DAILY, diltiazem 180 mg DAILY, or amlodipine 5 mg DAILY vs placebo plus atenolol 50 mg DAILY, diltiazem 180 mg DAILY, or amlodipine 5 mg DAILY	Posthoc analysis of CARISA trial Patients with chronic angina and diabetes (insulin- and non-insulin-dependent) compared with nondiabetic patients	N=823 12 weeks, followed by open-label extension study	Primary: Exercise tolerance Secondary: Time to onset of angina, time to ≥1 mm ST-segment depression, angina frequency, nitroglycerin usage, and HbA_{1c} levels in diabetic patients only and lipid panel as posthoc analysis	Primary: In the CARISA trial, 23% of the subjects were diabetic and 77% were not diabetic. The effects of ranolazine in the diabetic patients were comparable to those in the nondiabetic patients. There was no significant difference between the diabetic and nondiabetic patients in exercise duration (P=0.89), time to onset of angina (P=0.54), or time to ≥1 mm ST-segment depression (P=0.44). There was also no difference in the diabetic patients compared with the nondiabetic patients in angina frequency (P=0.81) or nitroglycerin consumption (P=0.063). Secondary: Compared with placebo, there were significant reductions in the HbA_{1c} levels in the ranolazine 750 mg (P=0.008) and ranolazine 1,000 mg (P=0.0002) treatment groups. A subgroup analysis showed that there were significant reductions in the HbA_{1c} levels in insulin-dependent diabetics treated with ranolazine (P=0.016 in the 750 mg group and P=0.008 in the 1,000 mg group). The non-insulin-dependent patients in the ranolazine-treated group showed a significant reduction in HbA_{1c} with the 1,000 mg dose (P=0.007), but not with the 750 mg dose (P=0.087). Treatment with ranolazine 750 mg was associated with an increase in low-density lipoprotein and total cholesterol, while treatment with ranolazine 1,000 mg did not have any effects on the lipids profile (no P values reported).
Cocco et al[23] Ranolazine 10, 60, 120 or 240 mg single dose in addition to their regular antianginal medication of a β-blocker or diltiazem	DB, MC, PC, RCT, XO Patients with chronic stable angina who remained symptomatic despite treatment	N=104 4-9 days	Primary: Exercise duration, time to angina, time to 1 mm ST-segment depression Secondary:	Primary: Exercise duration, time to angina, and time to 1 mm ST-segment depression were significantly improved with ranolazine 240 mg dose only in the β-blocker group and the groups combined (P<0.05 for both). There was no significant difference in exercise duration, time to angina, or time to 1 mm ST-segment depression with ranolazine treatment in patients that were on the diltiazem regimen (P>0.05 for all). Secondary: Treatment with ranolazine did not result in significant changes in heart rate or blood

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo in addition to patient's regular β-blocker or diltiazem	with β-blocker (atenolol, metoprolol, or propranolol) or diltiazem		Heart rate, blood pressure	pressure compared with placebo (P>0.05).
Pepine et al[24] Ranolazine immediate-release* 400 mg BID, 267 mg TID, or 400 mg TID vs placebo	DB, MC, PC, RCT, XO Patients with chronic stable angina that responded to conventional antianginal therapy	N=312 5 weeks	Primary: Time to angina onset, exercise duration, and time to 1 mm ST-segment depression at peak and trough concentrations Secondary: Safety	Primary: At peak ranolazine concentrations, time to angina onset (P≤0.02), exercise duration (P=0.013), and time to 1 mm ST-segment depression (no P value reported) were significantly improved with all dosing regimens. At trough ranolazine concentrations, only time to 1 mm ST-segment depression was significantly improved (P=0.047). Secondary: The rates of adverse effects were similar in the ranolazine groups and placebo group. Only minor gastrointestinal adverse effects were reported more frequently with ranolazine than placebo (6.6% to 10.7% vs 3.2%; no P value reported).
Koren et al[25] Ranolazine titrated to an optimal dose between 500 and 1,000 mg BID	MC, OL Patients who had completed the MARISA or CARISA trial, who were willing to participate in an open-label extension	N=746 Duration varied with a mean follow-up of 2.82 years	Primary: Discontinuation, adverse events, electrocardio-gram findings, and mortality Secondary: Not reported	Primary: 571 patients (76.7%) remained on therapy while 72 patients (9.7%) discontinued due to adverse events two years after initial dosing. There was a significant correlation between patient age >64 years and increased rates of discontinuation related to adverse events (RR, 2.32; P<0.001). A significantly lower correlation of adverse event-related discontinuation was seen in patients with a history of congestive heart failure (RR, 0.55; P=0.030). Compared to baseline, a mean prolongation of approximately 2.4 microseconds in the QT interval was observed (P<0.001). However there were no significant differences in PR or QRS intervals during this time (P value not reported.). A total of 64 deaths (all causes) occurred during the 2,102 patient-years (3.0% annual incidence) of the study. This translates to a 97.2% and 94.4%, 1- and 2-year survival from this incidence. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Rich et al[26] Ranolazine 750 mg vs ranolazine 1,000 mg vs placebo Ranolazine and placebo were administered BID in combination with diltiazem 180 mg DAILY, atenolol 50 mg DAILY or amlodipine 5-10 mg DAILY.	MA Patients with symptomatic chronic angina despite treatment	N=1,387 6 weeks	Primary: Improvement in younger patients (<70 years of age) and older patients (≥70 years of age) in exercise times, angina frequency, and adverse events Secondary: Not reported	Primary: Overall ranolazine significantly improved exercise duration and time to onset of angina during exercise testing ($P \leq 0.03$). There was no difference in ranolazine's effect on exercise time in younger patients compared to older patients ($P > 0.8$). Older patients tended to have fewer angina episodes (a mean of 3.21 in the placebo group and 2.08 in the ranolazine 1,000 mg group) than younger patients (a mean of 4.16 in the placebo group and 3.11 in the ranolazine 1,000 mg group). Adverse events were more commonly reported in the older patient population (32.6% in the placebo group and 44.2% in the ranolazine group) compared to the younger patients (31.2% in the placebo group and 32.1% in the ranolazine group). Secondary: Not reported
Morrow et al[27] MERLIN-TIMI 36 Ranolazine 200 mg intravenously* over 1 hour, followed by an 80 mg/hour intravenous infusion* continued for 12 to 96 hours followed by 1,000 mg orally twice a day until study completion vs	DB, MC, PC, RCT Patients 18 years of age or older with symptoms consistent with myocardial ischemia at rest, lasting more than 10 minutes and present within the previous 48 hours and had at least 1 of the following	N=6,560 Duration varied with a median follow-up of 348 days	Primary: Time to first occurrence of any element of the composite of cardiovascular death, myocardial infarction, or recurrent ischemia Secondary: Rate of major	Primary: In 21.8% of the patients in the ranolazine group and 23.5% of patients in the placebo group, the primary end point occurred (HR, 0.92; 95% CI, 0.83 to 1.02; P=0.11). In 10.4% of the patients in the ranolazine group and 10.5% of patients in the placebo group a cardiovascular death or myocardial infarction occurred (HR, 0.99; 95% CI, 0.85 to 1.15; P=0.87). In 13.9% of the patients in the ranolazine group and 16.1% of patients in the placebo group recurrent ischemia was reduced (HR, 0.97; 95% CI, 0.76 to 0.99; P=0.03). Secondary: Failure of therapy occurred in 36.8% of patients in the ranolazine group compared to 38.3% in the placebo group (HR, 0.94; 95% CI, 0.87 to 1.02; P=0.16).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
matching placebo Study medication was administered in addition to standard therapy.	indicators of moderate to high risk of death or recurrent ischemic events (elevated biomarkers of necrosis, ST depression of at least 0.1 mV, diabetes, or a TIMI risk score for unstable angina/non-ST-elevation myocardial infraction ≥3)		cardiovascular events (cardiovascular death, myocardial infarction, or severe recurrent ischemia), rate of failure of therapy (cardiovascular death, myocardial infarction, or severe recurrent ischemia), safety (death from any cause, symptomatic arrhythmias)	In 18.7% of patients in the ranolazine group compared to 19.2% of patients in the placebo group the secondary end point occurred (HR, 0.96; 95% CI, 0.86 to 1.08; *P*=0.50). There was no difference in the documented symptomatic arrhythmias in the ranolazine group (3.0%) and the placebo group (3.1%; *P*=0.84). There was no difference in the total mortality in the ranolazine group compared to the placebo group (172 vs 175; HR, 0.99; 95% CI, 0.80 to 1.22; *P*=0.91).
Scirica et al[28] MERLIN-TIMI 36 Ranolazine 200 mg intravenously* over 1 hour, followed by an 80 mg/hour intravenous infusion* continued for 12 to 96 hours followed by 1,000 mg orally twice a day until study completion vs	RCT Patients hospitalized with a non-ST-elevation acute coronary syndrome	N=6,351 7 days	Primary: Incidence of clinically significant arrhythmias (as monitored by ECG or Holter recording performed for the first 7 days after randomization) Secondary: Not reported	Primary: Ventricular arrhythmias: Ventricular tachycardia ≥3 beats ≥100 bpm was significantly less in the ranolazine group (52.1%) compared to placebo (60.6%) (RR, 0.86; 95% CI, 0.82 to 0.90; *P*<0.001). Ventricular tachycardia ≥4 beats ≥100 bpm was significantly less in the ranolazine group (20.9%) compared to placebo (29.5%) (RR, 0.71; 95% CI, 0.6 to 0.78; *P*<0.001). Ventricular tachycardia ≥8 beats (lasting <30 seconds) was significantly less in the ranolazine group (5.3%) compared to placebo (8.3%) (RR, 0.63; 95% CI, 0.52 to 0.76; *P*<0.001). There was no significant difference in polymorphic ventricular tachycardia ≥8 beats in the ranolazine group (1.2%) compared to placebo (1.4%) (RR, 0.83; 95% CI, 0.54 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
matching placebo Study medication was administered in addition to standard therapy.				1.28; *P*=0.40). There was no significant difference in sustained ventricular tachycardia (≥30 seconds) in the ranolazine group (0.44%) compared to placebo (0.44%) (RR, 1.01; 95% CI, 0.48 to 2.13; *P*=0.98). This includes monomorphic (0.13% vs 0.22%; RR, 0.59; 95% CI, 0.17 to 2.06; *P*=0.37) and polymorphic (0.32% vs 0.22%; RR, 1.41; 95% CI, 0.52 to 3.78; *P*=0.46). Supraventricular arrhythmias: There was no significant difference in new-onset atrial fibrillation in the ranolazine group (1.7%) compared to placebo (2.4%) (RR, 0.74; 95% CI, 0.52 to 1.05; *P*=0.08). Other supraventricular arrhythmias ≥120 bpm lasting at least 4 beats were significantly less in the ranolazine group (44.7%) compared to placebo (55.0%) (RR, 0.81; 95% CI, 0.77 to 0.85; *P*<0.001). Secondary: Not reported

*The immediate-release and injectable formulations of ranolazine are not available in the United States.
Drug regimen abbreviations: BID=twice daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RR=relative risk, XO=crossover
Miscellaneous abbreviations: bpm=beats per minute, CARISA=Combination Assessment of Ranolazine in Stable Angina, ERICA=Efficacy of Ranolazine in Chronic Angina, HbA_{1c}=glycosylated hemoglobin A1c, MARISA=Monotherapy Assessment of Ranolazine in Stable Angina, MERLIN-TIMI=Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes, SAQ=Seattle Angina Questionnaire, TIMI=thrombolysis in myocardial infarction

IX. Conclusions

The only agent classified as a miscellaneous cardiac drug is ranolazine. This agent is an antianginal drug that has been shown to significantly improve exercise duration, time to onset of angina, and time to 1 mm ST-segment depression. It also reduces angina frequency and nitroglycerin usage.[19-21] Ranolazine is approved for use in patients with chronic angina alone or in combination with β-blockers, nitrates, calcium channel blockers, anti-platelet therapy, ACE inhibitors, and ARBs.

Ranolazine has a different mechanism of action than currently available drugs to treat angina and does not cause hemodynamic changes such as reduction in blood pressure or heart rate.[3] The most common adverse effects were dizziness, nausea, asthenia, and constipation.[18-21] A significant concern with ranolazine is its potential for QT prolongation.[1] Therefore, caution should be used in patients with pre-existing QT prolongation or those who are taking QT-prolonging drugs.[2] Of note, in the MERLIN-TIMI 36 trial, ranolazine was not associated with an increased risk of arrhythmia or sudden death when given to patients experiencing an acute coronary syndrome.[11] Ranolazine should be avoided in patients taking potent CYP3A inhibitors/inducers or patients with a clinically significant hepatic impairment.[2]

Most current guidelines do not address the use of ranolazine, as it was approved after their publication dates or has not been approved in their host countries.[8-9,12] The ACC/AHA guideline on unstable angina and NSTEMI states that when used in accordance with its FDA-approved indication, ranolazine may be safely administered for symptom relief after UA/NSTEMI but it does not appear to significantly improve underlying disease.[7] The European Society of Cardiology does mention ranolazine in their Management of Stable Angina Pectoris guideline but no recommendations were issued concerning its use.[10] The European Society of Cardiology notes in their Management of ACS in Patients Presenting Without Persistent ST-segment Elevation guideline that ranolazine exerts antianginal effects by inhibiting the late sodium current and that it was not effective in reducing major cardiovascular events in the MERLIN-TIMI 36 trial.[11]

Currently there is limited data comparing ranolazine to other currently available antianginal agents such as β-blockers, calcium channel blockers, and long-acting nitrates. In one trial, Rousseau and colleagues demonstrated that the immediate-release formulation of ranolazine, when compared to atenolol, increased exercise duration. However, ranolazine proved similar to atenolol in its effect on other anginal symptoms such as time to angina, time to 1 mm ST-segment depression, angina frequency, and nitroglycerin use.[21]

X. Recommendations

In recognition of a mitigated proarrhythmia risk as observed in the MERLIN-TIMI 36 trial and the subsequent change in the product labeling information, it is recommended to remove a history of or an increased risk of QT prolongation and concurrent administration of drugs that may prolong the QT interval as contraindications from the current approval criteria. In addition, the list of medications that are contraindicated with concurrent Ranexa® use has been expanded to include CYP450 3A4 inducers (rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, St.John's wort).

It is recommended that Ranexa® use continues to require prior authorization with the following modified approval criteria:

- The patient has had a diagnosis/indication of chronic angina.

AND

- The patient has had a documented side effect, allergy, or treatment failure with at least one medication from two of the following classes: beta-blockers, maintenance nitrates, or calcium channel blockers.

AND

- The patient does not have any of the following conditions:
    - Hepatic insufficiency
    - Concurrent use of medications which may interact with Ranexa®:
        - CYP450 3A4 inducers (rifampin, rifabutin, rifapentin, phenobarbital, phenytoin, carbamazepine, St.John's wort)
        - CYP450 3A4 inhibitors (diltiazem, verapamil, ketoconazole, protease inhibitors, grapefruit juice, macrolide antibiotics)
        - Note: doses of digoxin or drugs metabolized by CYP450 2D6 (TCAs, some antipsychotics) may need to be adjusted if used with Ranexa®.

AND

- The medication requested has been prescribed or recommended by a cardiologist

AND

- The dose requested does not exceed 3 tablets/day (500 mg) or 2 tablets/day (1000 mg).

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